

2. The risk of developing esophageal cancer with the use of other forms of tobacco, such as pipe and cigar smoking, is about the same order of magnitude as that for cigarette smokers.

3. Epidemiological studies also indicate a synergistic relationship between the use of alcohol and tobacco and the development of cancer of the esophagus.

4. Experimental studies show that chemical compounds found in cigarette smoke are capable of inducing carcinoma of the esophagus in experimental animals. In some experimental models, esophageal carcinogenesis is enhanced if the carcinogen is dissolved in a dilute alcohol solution.

Cancer of the Urinary Bladder and Kidney

Bladder Cancer

Most cancers of the urinary bladder are transitional or squamous cell carcinomas which appear either alone or in combination. Unless these produce hematuria or obstruct the bladder outlet, they remain undiagnosed until quite late, making a cure unlikely. For patients diagnosed with bladder cancer from 1960 to 1973, the 5-year survival rate was approximately 60 percent for whites and 30 percent for nonwhites (240). The average annual incidence for males is about three times that for females, but this ratio may change as the larger proportion of women who are now smoking reach the age where bladder cancer rates are high (38).

The National Center for Health Statistics reported that there were 9,673 deaths from bladder cancer in the United States in 1976. There were 6,759 deaths among males, and 2,914 deaths among females (150). It is estimated that 9,900 people died of bladder cancer in 1978 (4).

Epidemiological Studies

Epidemiological data on the relationship between smoking and cancer of the urinary bladder have been accumulating for well over 20 years. Bladder cancer mortality ratios from the larger prospective epidemiological studies are summarized in Table 19. On the average, cigarette smokers are about twice as likely to die from cancer of the bladder as nonsmokers.

There have been numerous retrospective studies of the effect of smoking on cancer of the bladder (5, 36, 38, 41, 55, 101, 102, 124, 125, 147, 186, 195, 207, 240, 251, 253, 255). Several of these studies show a positive dose-response relationship between the number of cigarettes smoked per day, the duration of cigarette smoking or the lifetime number of cigarettes smoked, and an increased risk of developing bladder cancer.

TABLE 19.—Bladder cancer mortality ratios—prospective studies

Population	Study size	Non-smokers	All cigarette smokers	Comments
ACS Males in 9-State Study(68)	187,783 White Males	1.00	2.00	Smokers of 10-20 cigarettes Includes all urinary tract cancers. Includes Prostate.
British doctors(47a)	34,000 Male Doctors	1.00	2.11	
Canadian Veterans(20)	78,000 Males	1.00	1.40	Genitourinary cancers considered as a group
ACS 25 State Study(65)	1,000,000 Males and Females	1.00 1.00	2.00 (Males 45-64) 2.96 (Females 65-79)	
U.S. Veterans(90)	2,265,000 Person-Years	1.00	2.15	
California Males in 9 occupations(228)	68,158 Males	1.00	2.89	
Japanese study(77a,80)	265,118 Males and Females	1.00 1.00	1.36 (Males) 2.71 (Females-P. 0.05)	
Swedish Study(32)	55,000 Males and Females	1.00 1.00	1.80 (Males) 1.60 (Females)	Bladder + other urinary organs

Wynder and Goldsmith (240) reported that the risk of developing bladder cancer decreased among ex-smokers and approached that of nonsmokers about 7 years after quitting smoking.

Several authors have calculated the percentage of bladder cancers which can conservatively be attributed to the cigarette smoking habit. Wynder and Goldsmith (240) estimated that 40 percent of male bladder cancers and 31 percent of female bladder cancers may be attributed to smoking cigarettes. This is in agreement with the estimates by Cole, et al. (38) of 39 percent in males and 29 percent in females.

In a cohort analysis of men and women in the United States, Denmark, England, and Wales, Hoover and Cole (87) examined the strength of the association between cigarette smoking, the development of bladder cancer, and successive birth cohorts. Increasing rates of bladder cancer were observed in populations characterized by an

increase in cigarette smoking among successive birth cohorts. The association was consistent in both men and women and was also found for different nationalities and for urban and rural groups. These findings are consistent with a causal role for cigarette smoking in the development of bladder cancer. It is interesting that the cohort analysis for bladder cancer is similar to and parallels that of cancer of the pancreas.

Other Risk Factors

Certain occupational exposures are associated with an increased risk of developing bladder cancer. Those who work with dyestuffs, rubber, leather, print, paint, petroleum, and other organic chemicals are particularly at risk. The common denominator appears to be aromatic amines. A number of specific carcinogens for the human bladder have been identified, including aminobiphenyl, 2-naphthylamine, benzidine, 1-naphthylamine, and 4-nitrobiphenyl (35). Some of these compounds are found in cigarette smoke. The relationship between cigarette smoking and occupational exposure is complex. It is likely that cigarette smoking can act as a sole agent in the development of bladder cancer; however, there may also be synergistic interactions between cigarette smoking and occupational exposures.

Animal Studies

Numerous experiments have been undertaken to examine the relationship of tobacco smoking to bladder carcinogenesis. The areas of major concern have centered upon aromatic amines, nitrosamines, tryptophan metabolism (107) and, more recently, non-nutritive sweetness, as in saccharin and cyclamates. The effect of these classes of compounds on the etiology of bladder cancer in experimental animals has been extensively reviewed in the literature.

Kidney Cancer

For 1978, the estimated incidence of kidney and other urinary cancers, exclusive of cancer of the bladder, was 9,400 for males and 5,700 for females. The estimated number of deaths for these same cancers was 4,600 in males and 2,800 in females (4). The 5-year survival rate following the diagnosis of kidney cancer is 40 to 50 percent (151).

Epidemiological Data

In most of the prospective studies, cancer of the kidney refers to tumors arising from the renal parenchyma as well as tumors in the renal pelvis and ureter. In some of the retrospective investigations, tumors at these various sites are considered separately in relationship to cigarette smoking. In several of the large prospective epidemiological studies, an association was found between cigarette smoking and

**TABLE 20.—Kidney cancer mortality, ratios and relative risks:
selected prospective and retrospective studies**

Population	Study size and type	Number of kidney cancer deaths	Mortality ratio or relative risk ratio		Comments
			Non smokers	Cigarette smokers	
ACS 25 State Study(65)	440,558 males. Prospective study	104	1.00	1.42 1.57	Age 45-64 Age 65-79
U.S. Veterans(90)	2,265,000 person years. Prospective study	141	1.00	1.45	
California Males in 9 Occupations(228)	68,153 males. Prospective study	27	1.00	2.46	
Japanese study(77a)	122,261 males. Prospective study	30	1.00	1.20	
Bennington, Laubscher(16a,17)	Retrospective study of renal adenocarcinoma. 100 cases 190 controls	100	1.00	5.1	Risk ratio for Pipe - 10.3 Cigar - 12.9
Schmauz Cole(180)	Retrospective study. 43 cases of renal pelvis or ureter. 451 controls	18	1.00	10.0	For smokers of more than 2 1/2 pks/day
Armstrong(8)	Retrospective study. 106 adenocarcinoma of kidney. 30 carcinoma of renal pelvis. 139 controls	106 30	1.00 1.00	1.06 1.80	
Wynder et al.(248a)	Retrospective study 202 adenocarcinoma of kidney. 394 controls.		1.00 1.00	2.00 1.50	(Males) (Females)

cancer of the kidney. The mortality ratios for all cigarette smokers varied from 1.42 to 2.46, compared to nonsmokers. The results of these studies are summarized in Table 20.

**TABLE 21.—Kidney cancer mortality ratios, by amount smoked:
U.S. Veterans Study**

Cigarettes smoked per day	Mortality ratios	Number of deaths
Nonsmokers	1.00	39
1-9	0.97	4
10-19	1.34	21
20-39	1.68	16
40+	2.75	5
All cigarette smokers	1.45	46

SOURCE: Kahn, H.A. (90)

Earlier retrospective reports of the association of renal adenocarcinoma with smoking reported a relative risk ratio of about 5.0 for cigarette smokers compared to nonsmokers (16, 17). They did find a positive association between cigarette smoking and cancer of the renal pelvis, as had Schmauz and Cole (180). Wynder, et al. (248) reported a moderate but significant association between cigarette smoking and renal adenocarcinoma for both males and females. There were positive dose-response relationships with the number of cigarettes smoked per day. The results of these studies are summarized in Table 20. A dose-response relationship with the number of cigarettes smoked per day was also found in the study of U.S. veterans (Table 21).

Conclusions

1. Epidemiological studies demonstrate a significant association between cigarette smoking and cancer of the urinary bladder in both men and women. Supporting evidence from other disciplines supports the conclusion that cigarette smoking is one of the causes of cancer of the urinary bladder.

2. Epidemiologic studies show a positive dose-response relationship for developing bladder cancer with increases in the number of cigarettes smoked per day.

3. Cigarette smoking acts independently as a cause of bladder cancer and probably acts synergistically with other risk factors for bladder cancer, such as occupational exposure to certain aromatic amines.

4. Epidemiological studies have demonstrated an association of cigarette smoking with cancer of the kidney among men. There is some evidence of a dose-response relationship with the number of cigarettes smoked per day in the development of kidney cancer.

Cancer of the Pancreas

The National Center for Health Statistics reported that there were 19,738 deaths from cancer of the pancreas among men and women in the United States in 1976 (150). Deaths from cancer of the pancreas were expected to exceed 20,000 in the United States during 1978 (4). The incidence of cancer of the pancreas has increased threefold since 1930 (100, 111), and it now ranks fourth in frequency among fatal neoplastic diseases (187).

The most common form of pancreatic cancer in humans is adenocarcinoma, which originates from the epithelial duct cells of the pancreas. Acinar and islet cell tumors are relatively rare. Because of an extensive venous and lymphatic drainage system, metastases can occur relatively early in the course of the disease, contributing to the poor 3-year survival rate of 2 percent (152). Morgan and Wormsley (149) have reported that most studies have shown a mean survival time after diagnosis of less than 6 months.

Pancreatic cancer is more common among men than women in the United States, but the male-to-female ratio has been decreasing steadily from 1.6:1 during the period of 1940 to 1949 to 1.3:1 observed from 1965 to 1969 (152).

Epidemiological Studies

Several prospective epidemiologic investigations (20, 32, 65, 79, 80, 90, 228) have reported mortality ratios for cigarette smokers of approximately 2.0, compared to nonsmokers. These data are presented in Table 22. Not all of these investigations demonstrate a dose-response relationship with the number of cigarettes smoked per day; this is probably due to the small number of deaths in each smoking category. In a retrospective case control study with 81 cases of cancer of the pancreas, Wynder, et al. (248) showed a definite dose-response relationship with a relative risk of 5.0 for males smoking more than two packs of cigarettes a day. These data are presented in Figure 8. The dose-response data from the Swedish study are presented in Table 23.

Pancreatic cancer mortality in the United States was examined by cohort analysis for the period 1939 to 1969 by Bernarde and Weiss (16). White men were found to be at greater risk of developing pancreatic cancer than white women, and the same relationship existed for nonwhites. With the passage of time, there was a shift of the cohort mortality rate curve by age toward younger groups. These data appear to be compatible with an hypothesis which relates environmental factors to the etiology of pancreatic cancer. Air and water pollution, ionizing radiation, and improved diagnosis are unlikely to explain the observed differences, because these factors would be expected to influence both race and sexes more or less equally. Cigarette smoking,

**TABLE 22.—Pancreatic cancer mortality ratios—
prospective studies**

Study population	Size of population	Nonsmokers	All cigarette smokers
Canadian veterans (80)	78,000 males	1.00	1.96
A.C.S. 25-State Study (65)	440,000 males	1.00	2.69
U.S. veterans (90)	239,000 males	1.00	1.84
Japanese study (77a,80)	122,000 males	1.00	1.41 males
	143,000 females	1.00	1.94 females
California occupations (228)	63,000 males	1.00	2.43
Swedish study (32)	55,000 males and	1.00	3.1 males
	females	1.00	2.5 females

high risk occupations, and dietary practices are more likely to explain these differences. Cigarette smoking is an exposure which is closely related to cohort and sex difference.

Other Risk Factors

There is epidemiologic evidence which links pancreatic cancer with increased dietary fat and protein intake (80, 228). An increased incidence of pancreatic cancer has been observed in chemists and industrial workers exposed to beta naphthylamine (131). A survey of death certificates of member chemists of the American Chemical Society indicates an increased relative frequency of pancreatic cancer (120). However, specific chemical exposures could not be traced.

Animal Studies

There are relatively limited numbers of experimental laboratory studies concerning cigarette smoking and cancer of the pancreas. Pour, et al. (112, 166), using a nitrosamine compound, induced pancreatic neoplasms in hamsters which were histologically similar to those in humans. Although the particular nitrosamine used in these experi-

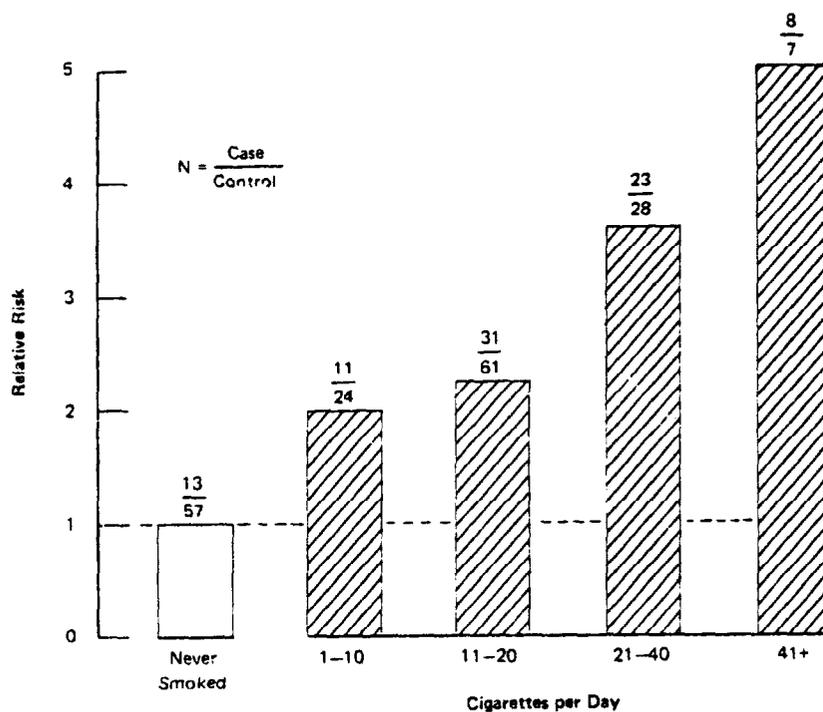


FIGURE 8.—Relative risk of pancreatic cancer in males, by number of cigarettes smoked

SOURCE: Wynder, E.L. (248)

TABLE 23.—Mortality ratios for cancer of the pancreas among Swedish subjects, aged 18-69, by sex and amount smoked

Number of cigarettes per day	Males	Females
Nonsmokers	1.0	1.0
1-7	1.6	2.4
8-15	3.4	2.5
15+	5.9	3.0
All cigarette smokers	3.1	2.5

SOURCE: Cederlof, R. (32)

ments is not found in tobacco smoke, a number of other nitrosamine compounds, such as dimethyl nitrosamine and methylethyl nitrosamine,

have been found in cigarette smoke (81). This points to a class of compounds which should be investigated for their carcinogenic potential in cancer of the pancreas.

Konturek, et al. (108) has reported that nicotine inhibits pancreatic bicarbonate secretion in the dog by direct action on the organ. This has led to speculation that inhibition of duct cell secretion of bicarbonate could lead to intracellular pH changes and subsequently play a role in carcinogenesis.

Conclusions

1. Epidemiological data from prospective and retrospective investigations have demonstrated a significant association between cigarette smoking and cancer of the pancreas.

2. Several epidemiological studies contain evidence of a dose-response relationship for the number of cigarettes smoked per day. The relative risk of developing cancer of the pancreas is about five times greater for a two-pack-a-day smoker than for a nonsmoker.

Mechanisms of Carcinogenesis

Smoke Composition

Cigarette smoke for use in experimental studies is usually separated into a gas phase and a particulate phase by passing whole smoke through an appropriate filter. The compounds retained by the filter constitute the particulate phase and are referred to as "tar." More than 2,000 compounds have been identified in cigarette tar. The gas phase, which makes up more than 90 percent of the volume of whole smoke, contains a much smaller number of compounds. The particulate phase can be subdivided into categories based on the solubility of the compounds in acid, neutral, or basic solvents. Most of the chemical compounds which participate in the induction and maintenance of the malignant process are contained in the neutral portion of the particulate phase. A detailed analysis of the components of cigarette smoke is presented in the Chapter on the Constituents of Tobacco Smoke. This subject has also been reviewed in detail by Hoffmann and Wynder (83).

Experimental Models

Cigarette smoke, whole tobacco tars, the gas phase of cigarette smoke, various tobacco condensate subfractions, and single or multiple compounds known to be present in tobacco smoke have been used in studying the mechanisms of carcinogenesis in experimental animals. Rats, mice, hamsters, guinea pigs, rabbits, dogs, monkeys, donkeys, chickens, and other animals have been used in studying the carcinogenic properties of tobacco smoke.

It has not been possible to duplicate the same conditions of smoke inhalation in experimental animals as are found in humans. Many animals are obligate nose breathers, and under these circumstances turbulent precipitation of smoke particles in the nasal passages prevents most of the active compounds from reaching the lungs. A variety of alternate approaches have been used. The painting of shaved mouse skin with whole tobacco tar and various chemical constituents has been widely used. Other investigators have used subcutaneous injection, intratracheal instillation, implantation, and feeding. Tissue and organ cultures have also been used to study carcinogenesis. Chapter 14 contains a more complete discussion of this subject.

Concepts of Carcinogenesis

Carcinogenesis is a complex process involving multiple steps and various compounds operating at different points in the sequence. Chemical compounds have been classified as to the respective roles they play in the process of carcinogenesis. Cigarette smoke and tobacco tar act as complete carcinogens, since no additional compounds or steps are necessary to induce malignant changes in a variety of animal systems. When individual chemical compounds and subfractions are examined, however, the process of carcinogenesis becomes increasingly complex. Chemicals which can induce the first steps of malignant transformation are known as carcinogens or tumor initiators. Tumor promoters are compounds which continue the process of tumor formation when they are applied to tissue following initial treatment with a chemical carcinogen (23). Compounds known as co-carcinogens exert their effects when administered simultaneously with carcinogens or tumor initiators. Compounds which act as co-carcinogens do not necessarily have tumor-promoting properties. Mouse skin is frequently used for identifying co-carcinogens as well as promoters (85). Catechol is a potent co-carcinogen but is inactive as a tumor promoter. On the other hand, phenol, a tumor promoter, has no known co-carcinogenic activity (219). Data such as these support the idea that tumor promotion and co-carcinogenesis are independent phenomena with distinct mechanisms of action. Both promoters and co-carcinogens play an important role in tumor induction by tobacco products (161).

Additionally, Hoffmann and Wynder (82, 244) have described the property of tumor acceleration possessed by N-alkylated carbazoles and certain other compounds. These compounds are inactive as complete carcinogens, initiators, or promoters but accelerate the initiator-promoter activity of polynuclear aromatic hydrocarbons.

The carcinogens, tumor promoters, and ciliotoxic agents which have been identified in the gas phase of tobacco smoke are listed in Table 24. The major carcinogenic agents which have been identified in the particulate phase of tobacco smoke are listed in Table 25. The first part of Table 25 lists the 17 agents which are identified as tumor initiators;

TABLE 24.—Carcinogenic, promoting, and ciliotoxic agents in the gas phase of tobacco smoke*

Smoke compounds	Amount in smoke of one cigarette
I. Carcinogens†	
$\begin{array}{c} \text{H}_3\text{C} \\ \quad \diagdown \\ \quad \text{N} - \text{NO} \\ \quad \diagup \\ \text{H}_3\text{C} \end{array}$	Dimethylnitrosamine 5-180ng**
$\begin{array}{c} \text{R} \\ \quad \diagdown \\ \quad \text{N} - \text{NO} \\ \quad \diagup \\ \text{R}' \end{array}$	Dialkylnitrosamines (4 compounds) 2-80ng
	Nitrosopyrrolidine 1-110ng
	Nitrosopiperidine 0-9ng***
$\begin{array}{l} \text{H}_2\text{N} - \text{NH}_2 \\ \text{E}_2\text{C} - \text{CHCl} \end{array}$	Hydrazine Vinyl chloride 24-43ng 6-16ng
II. Tumor promoters	
HCHO	Formaldehyde 20-90μg
III. Ciliotoxic agents	
HCN	Hydrogen cyanide 100-700μg
HCHO	Formaldehyde 20-90μg
H ₂ C-CH-CHO	Acrolein 45-140μg
H ₃ C-CHO	Acetaldehyde 18-1,440μg

*List is based only on publications with unambiguous identifications of tumorigenic smoke compounds.

†Tobacco smoke is suspected of also containing H₂As (arsine), Ni(CO)₄ (nickel carbonyl) and possibly other volatile chlorinated olefins than vinylchloride and nitro-olefins.

**ng = 10⁻⁹g

***μg = 10⁻⁶g

SOURCE: Wynder, E.L. (243)

the second part contains a list of organ-specific carcinogens. The tumor promoters and co-carcinogens found in the particulate phase of tobacco smoke are listed in Table 26.

Many chemical carcinogens or initiators must be partially metabolized before they can exert their carcinogenic effects. Of the chemical carcinogens present in cigarette smoke, the metabolism of the polyaromatic hydrocarbons (PAH), in particular benzo(a)pyrene, has been most widely studied. The enzyme, aryl hydrocarbon hydroxylase (AHH), is responsible for the conversion of PAH into a number of hydroxylated derivatives (60, 91, 191).

TABLE 25.—Carcinogenic agents in the particulate phase of tobacco smoke¹

Smoke compounds		Amount in smoke of one cigarette
Tumor Initiators ²	Biol. Act. ²	
Benzo(a)pyrene	(+++)	10-50ng
5-Methylchrysene	(+++)	0.6ng
Dibenz(a,h)anthracene	(++)	40ng
Benzo(b)fluoranthene	(++)	30ng
Benzo(j)fluoranthene	(++)	60ng
Dibenzo(a,h)pyrene	(++)	present
Dibenzo(a,i)pyrene	(++)	present
Dibenz(a,j)acridine	(++)	3-10ng
Indeno(1,2,3-cd)pyrene	(+)	4ng
Benzo(a)anthracene	(+)	40-70ng
Chrysene	(+)	40-60ng
Methylchrysenes	(+)	13ng
Methylfluoranthenes	(+)	50ng
Dibenz(a,c)anthracene	(+)	present
Dibenz(a,h)acridine	(+)	0.1ng
Dibenzo(c,g)carbazole	(+)	0.7ng
Benzo(c)phenanthrene	(+)	present
Organ specific carcinogens ³		
A. Esophagus		
N ² -Nitrososornicotine		140ng
Nitrosopiperidine		0-9ng
Nitrosopyrrolidine		1-110ng
Unknown Nitrosamines		?
B. Lung		
Polonium-210		0.03-1.3pCi ⁴
Nickel compounds		0-600ng
Cadmium compounds		9-70ng
Unknowns		?
C. Pancreas		
Nitrosamines		?
Unknowns		?
D. Kidney and Bladder		
β -Naphthylamine		22ng
x-Aminofluorene		present
x-Aminostilbene		present
o-Toluidine		present
Unknown Aromatic Amines		?
o-Nitrotoluene		21 μ g
Unknown Nitro compounds		?
Di-n-butyl nitrosamine		0.3ng
Unknown nitrosamines		?

¹So far with certainty identified.

²Biol. Act. = Relative carcinogenic activity on mouse skin. +++ highly active; ++ moderately active; + weakly active.

³These carcinogens also may act on other target organs

⁴pCi = picoCurie, 10⁻¹²Curie

SOURCE: Wynder, E.L. (245)

TABLE 26.—Tumor promoters and co-carcinogens in the particulate phase of tobacco smoke¹

Smoke compounds	Amount in smoke of one cigarette
Tumor promoters	
Volatile phenols	150-500µg
Unknown weakly acidic compounds	?
Unknown neutral compounds	?
Co-carcinogens	
Pyrene	50-200ng
Methylpyrenes	30-300ng
Fluoranthene	100-260ng
Methylfluoranthenes	180ng
Benzo(ghi)perylene	60ng
Benzo(e)pyrene	30ng
Other PAH	?
Napthalenes	0.3-6.3µg
1-Methylindoles	0.83µg
9-Methylcarbazoles	0.14µg
4,4'-Dichlorostilbene	1.5µg ²
Other neutral compounds	?
Catechol	200-500µg
4-Alkylcatechol	10µg
Other acidic compounds	?

¹So far with certainty identified.

²Values are decreasing because of lesser use of DDT and DDD for tobacco cultivation.

SOURCE: Wynder, E.L. (243)

Aryl Hydrocarbon Hydroxylase

AHH activity is present in most tissue of the body. It is induced by treatment *in vivo* or *in vitro* with a variety of PAH or related chemicals. Tobacco smoke inhalation elevates AHH activity in respiratory tissues of laboratory animals (2, 51, 231) and in human peripheral lymphocytes and pulmonary alveolar macrophages (29, 129). Inducible levels of the enzyme vary both with the tissue and with the individual (60, 97, 156).

Kellermann, et al. (25, 96) reported that the percentage of lung and laryngeal cancer patients with highly inducible AHH levels was much greater than in the normal population. On the other hand, there have been reports in which the inducibility of AHH in lung cancer patients either did not differ significantly from controlled populations (123) or was lower than in controls (17). Further research is necessary to clarify the relationship between cigarette smoking, AHH inducibility, and the development of cancer.

Multi-Stage Model of Carcinogenesis

One unifying hypothesis is the multi-stage model of carcinogenesis. This model has been proposed in various forms by several scientists and has recently been given attention by Armitage (6), Doll (42), and Peto (165). In the multi-stage model, carcinogenesis is considered a disease of interactions.

The transformation of a normal cell to a malignant one would require two or more separate stages, each with a characteristic probability of occurrence determined by one or more of the carcinogens present. The initiation and development of cancer would thus be a multi-stage, multi-causal process, in which both external and internal factors act in a sequence of several steps before the cancer would appear clinically. The multi-stage concept of carcinogenesis offers a plausible explanation for some of the peculiarities of the induction of lung cancer (such as the multiplicative effect of asbestos on cigarette smokers and the changing risks of ex-smokers). It is likely that development of cancer in each organ or tissue requires a different set of factors to induce malignant changes. It should not be surprising that cigarette smoking can induce malignant changes in as many organ systems as it does. Evidently, among the 2,000 chemical compounds found in cigarette smoke, there are sufficient carcinogens, tumor initiators, co-carcinogens, and tumor promoters to induce cancer in multiple-organ systems. Certainly, over the long time period in which the smoker is exposed to the products of tobacco combustion, there is sufficient time to satisfy the most complex multi-phased or multi-causal process. Given this model, it is not surprising that tobacco carcinogenesis is additionally influenced by a number of environmental factors (76). This would explain the synergism for lung cancer observed in cigarette smokers in various occupations, such as asbestos workers and uranium miners.

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